REMARKS

Favorable reconsideration of this application is respectfully requested. Claims 1-23, 36, 44, 45, 85-92 and 96-99 are pending in this application. Claims 44, 86 and 99 are currently amended. Claims 17, 20, 21, 91 and 92 have been withdrawn from consideration.

The Examiner has indicated that the Information Disclosure Statement has been considered in part since references other than the U.S. references were not in the USPTO file. Applicants provide herewith the currently available documents. Consideration of these references is respectfully requested.

The Examiner has objected to claims 44-45, 85-89 and 99 as being unclear with respect to a desirable biological activity. It is submitted that independent claims 44, 86 and 89 as originally filed were clear and would have been understood by those skilled in the art. Nonetheless, in an effort to advance prosecution of this case, independent claims 44, 86 and 89 have been amended to clarify that the resulting immunoglobulin molecule or fragment thereof exhibits the biological activity of the biologically active peptide. No new matter has been added. Reconsideration of this rejection is requested.

Claims 1-16, 18-19, 22-23, 36, 44-45, 85-90, and 96-99 have been rejected under 35 U.S.C. §103(a) as obvious in light of Barbas *et al.* (WO 94/18221) (hereinafter "the Barbas PCT") in view of WO 96/40750 (hereinafter "Dower"), Barbas et al. (PNAS 92:2529-2533) (hereinafter "the Barbas Publication"), and Kini et al. (FEBS Letters 375:15-17, 1995) (hereinafter "Kini"). Applicants respectfully traverse this rejection and request that the Examiner reconsider the rejection in light of the comments below.

Independent claim 1 recites, *inter alia*, "a region where amino acid residues corresponding to at least a portion of a complementarity determining region (CDR) are replaced with a peptide mimetic selected from the group consisting of erythropoietin (EPO) mimetics and thrombopoietin (TPO) mimetics, wherein the immunoglobulin molecule or fragment thereof binds an EPO or TPO receptor." In other words, the immunoglobulin or fragment thereof includes an EPO or TPO peptide mimetic to facilitate binding of the immunoglobulin or fragment thereof to an EPO or TPO receptor. The applied references, taken alone or in combination, fail to teach or suggest such a composition.

Barbas PCT is a generic disclosure of incorporating a "binding site" into a CDR. This generic disclosure provides no motivation or suggestion whatsoever that it is desirable, practical, or even possible to incorporate the specifically recited EPO and TPO mimetics into the immunological molecule or fragment(s) thereof. Moreover, the Examiner correctly noted, Barbas PCT does not teach replacing a CDR with a TPO mimetic of SEQ ID NO: 2 or SEQ ID NO:1 with proline flanking the sequence . . . or the scaffold is the anti-tetanus toxoid antibody. Accordingly, the Barbas PCT application fails to disclose incorporation of a TPO or EPO mimetic into an immunoglobulin molecule as recited by claim 1.

Applicants respectfully disagree with the portion of the Office Action alleging Barbas PCT teaches that other sequences for other receptors would also work in replacing CDRs to the extent that the Office Action argues that "other sequences" provides motivation to successfully use EPO or TPO sequences for binding to EPO or TPO receptors. Rather, Barbas PCT describes such "other sequences for other receptors" as, *inter alia*: non-RGD-dependent integrin binding sites; HIV Gp120 binding sites; EBV gp350/220 binding sites; as well as other binding sites

including insulin receptor binding sites, reovirus binding sites, fibrinogen receptor binding sites, and thyroid hormone receptor binding sites. See pages 24-27. Nowhere is there any suggestion or mention of using an EPO or TPO peptide mimetic which binds an EPO or TPO receptor as required by the claim 1.

Barbas PCT is directed solely to teaching grafting peptides into a CDR region of an antibody to yield an antibody with antagonistic properties. Thus, Barbas PCT relates to antibodies which may merely bind and block the target to which they binds such that the bound site cannot bind to another entity. See page 147, lines 34 through page 148, line 2 where it states: "Thus, this invention demonstrates potential for using CDR's as a design template for obtaining inhibitory CDR-derived peptides." This make clear that Barbas PCT relates to antibodies having inhibitory properties. Applicants' antibodies are distinguishable from that of Barbas PCT in that they have agnostic properties, i.e. bind to a target while retaining the activity of the engrafted peptide such that the grafted antibody has an actual activity, and is not merely binding to and blocking a binding site. Accordingly, claim 1 is not obvious in light Barbas PCT when taken alone.

Applicants respectfully disagree with the portion of the Office Action alleging that the deficiencies of Barbas PCT are made up for in the teachings of Dower, the Barbas Publication and Kini.

Dower fails to cure this deficiency of Barbas PCT. Nowhere does Dower teach or suggest that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. Dower is limited to low molecular weight peptides and peptide mimetics. (See the paragraph bridging pages 4 and 5

Dower.) Being specifically limited to "defined *low molecular weight* peptides and peptide mimetics", Dower lacks any teaching with respect to immunoglobulin molecules or fragments that bears on the obviousness of claim 1 and the claims that depend therefrom.

Applicants respectfully disagree with the portion of the Office Action alleging that because Dower specifically teaches SEQ ID NO: 1 and peptides that are fusion proteins and the peptides need to be constrained to be active that one of ordinary skill in the art would be motivated to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO: 2 in one or two CDRs of the heavy or light chain of the antibody . Conversely, the proposed modification of adding the mimetics of Dower to the immunoglobulin of Barbas PCT would likely render Dower unsatisfactory for its intended purpose of making defined low molecular weight peptides and peptide mimetics having strong binding properties to the TPO-R. (See page 4, Summary of the Invention). As Dower is limited to low molecular weight peptides and peptide mimetics, Dower teaches away from using the larger molecular weight proteins of Barbas PCT. Accordingly, using higher molecular weight proteins in Dower would render Dower unsatisfactory for its intended purpose and there can be no motivation to combine the references. In any obviousness rejection based on a combination of references, there must be some suggestion or motivation provided ***in the references*** to combine them in the manner described in the rejection to arrive at applicants' claimed invention. Here there is clearly no such suggestion or motivation to combine the low molecular weight proteins of Dower with the high molecular weight proteins of Barbas PCT, and claim 1 is not obvious.

The Barbas Publication fails to cure the deficiencies of Barbas PCT. Nowhere does the Barbas Publication teach or suggest that it is desirable, practical or even possible to incorporate

the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. Rather, the Barbas Publication is limited to replacement of various HCDR3 sequences for Fabs SI-1, SI-40, and SI-32, and the like grafted onto the heavy chain of an anti-tetanus toxoid Fab, replacing the existing HCDR3, by overlap extension PCR. See for example, column 2. There is no mention of an EPO or TPO mimetic being added to an immunoglobulin or fragment thereof. Accordingly, one would not be motivated to combine this reference teaching with Barbas PCT, which also fails to mention EPO or TPO mimetics, to arrive at the claimed invention which requires an EPO or TPO mimetic. Accordingly claim 1 is not obvious.

Applicants respectfully disagree with the portion of the Office Action alleging that because the Barbas Publication teaches replacement in the anti-tetanus antibody of unrelated sequences from that in the CDR and the antibody binds the target and since antibody tertiary structures are homologous one skilled in the art would conclude that the anti-tetanus antibody could be used for presentation of other sequences. In any obviousness rejection based on a combination of references, there must be some suggestion or motivation provided ***in the references*** to combine them in the manner described in the rejection to arrive at applicants' claimed invention. Here there is clearly no such suggestion or motivation to substitute the sequences grafted onto the heavy chain of an anti-tetanus toxoid Fab of Barbas B with the EPO and TPO mimetics, and incorporate the mimetics into the proteins of Barbas PCT, and claim 1 is not obvious.

Kini fails to cure this deficiency of Barbas PCT because it fails to mention EPO or TPO mimetics as required by the claim 1. Conversely, Kini relates to incorporating proline residues on either or both sides of the interaction site of an antiplatelet peptide, IARGDMNA and

determined the inhibitory potency of the peptides in whole blood. Accordingly, Kini is limited to adding prolines to the ends of short peptides, and does not teach adding prolines to a peptide that is inserted into the middle of a large protein such that the inserted proline has very long flanking sequences, not merely one or two amino acids added to the ends. Accordingly modifying Kini to incorporate the smaller peptides into larger peptides would render Kini unsatisfactory for its intended purposes. At the last paragraph in the left-hand column of page 16, Kini teaches away from the present invention by stating, "In small peptides, containing the minimum molecular recognition sites, since there are no adjacent secondary structures, proline brackets probably help in the presentation of the site. In these peptides, the lack of secondary structure-stabilizing features, such as reinforcing hydrogen bonds, prevent definite secondary structures, and the peptides occur in many relatively unstable configurations." This teaches away from the current invention wherein the EPO and TPO mimetics are placed within an immunoglobulin molecule or fragment thereof. Kini adds prolines to the ends of very short peptides to give them a definite secondary structure, but such should not be needed when the peptide is placed in the middle of a large protein. Accordingly, the reasoning of Kini no longer applies and it has been surprising found by Applicants that the use of surrounding prolines increases the activity even when the peptide is placed in the middle of a large protein. Accordingly, claim 1 is not obvious.

For at least the foregoing reasons, Barbas PCT, Dower, the Barbas Publication and Kina, taken alone or together, fail to teach or suggest the composition of independent claims 1. Accordingly, withdrawal of the rejection claims 1 under 35 U.S.C. §103(a) as well as any of the

claims that depend therefrom (i.e. claims 2-16, 18-19, 22-23 & 36) is deemed appropriate and is respectfully requested.

Turning now to the claims wherein the biologically active peptide inserted into an immunoglobulin molecule or fragment is flanked with a proline at the carboxy terminus (i.e., claims 19, 44, 45, 85, 87-89 and 96), none of the applied references teaches or discloses that the presence of a proline at the carboxy terminus of the ***inserted*** biologically active peptide is particularly useful compared to any other amino acid at that position. Applicants respectfully disagree with the portion of the Office Action alleging Kini provides strong motivation and teaches adding a proline residue at the C-terminus of the peptide.

It has been surprisingly found by Applicants that a proline flanking the peptide can provide an increase ***in biological activity of the inserted biologically active peptide***. It is these various proline-extended embodiments that are embraced by claims 19, 44, 45, 85, 87-89 and 96. The extensive data presented in the working examples of Applicants' specification support the conclusion that proline extension provides a beneficial and unexpected result compared to other amino acids at the carboxy terminus. The conclusion supported by the data is summarized in the paragraph bridging pages 45 and 46 of Applicants' specification as follows:

> "All clones which demonstrated strong binding, were found to contain a proline just downstream of the 14 amino acid TPO mimetic peptide. Selection by panning of a proline in the downstream linker position represents determination of a surprising amino acid choice which confers improved binding characteristics to the grafted TPO mimetic peptide. Weak binders did not contain this proline although they still contained the TPO mimetic peptide."

Clearly, there is no appreciation in the Barbas PCT application or any of the other applied references that the presence of a proline at the carboxy terminus has any particular effect on a peptide ***inserted at a CDR of an immunoglobulin***. As stated above, Kini relates to

incorporating proline residues on either or both sides of the interaction site of an antiplatelet peptide, IARGDMNA and determined the inhibitory potency of the peptides in whole blood. Accordingly, Kini is limited to adding prolines to the ends of short peptides, and does not teach adding prolines to a peptide that is inserted into the middle of a large protein such that the inserted proline has very long flanking sequences, not merely one or two amino acids added to the ends. In any obviousness rejection based on a combination of references, there must be some suggestion or motivation provided ***in the references*** to combine them in the manner described in the rejection to arrive at applicants' claimed invention. Here there is clearly no such suggestion or motivation in any of the references. If it is the examiner's position that there is some motivation or suggestion in the Kini reference to insert a biologically active peptide flanked with a proline at the carboxy terminus into or in place of an antibody CDR, the examiner is respectfully requested to point out with particularity (by page/column and line) where in Kini such a teaching can be found. Applicants respectfully submit that no such motivation can be found in any of the applied references and that absent a suggestion in the references, the present rejection is improper and should be withdrawn.

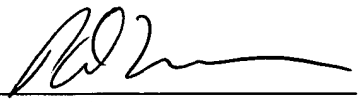
With respect to claims 86 and claims 97-99, the Office Action contends a clearer citation is on page 86 wherein the RGD sequence was the peptide sequence and three amino acids on each side were added (see page 86, lines 1-7), thereby disclosing 2 flanking amino acids. Applicants disagree with this reading of the Barbas PCT application. The 3 amino acids on page 86 were further bordered by the nucleotide sequence for encoding the 5' and 3' CDR3 amino acid residues present in the pMT12 expression vector. Thus, the reference to 3 nucleotides on page 86 does not teach or suggest 2 flanking amino acids as that phrase is used in claims 86 and

97-99. Furthermore, Applicants note that claim 86 was written in a Markush format, and Barbas PCT fails to show the selected combinations of amino acids. Accordingly claims 86 and 97-99 are believed to be immediately allowable.

Amended Claims 44, 86 and 99 distinguish over the applied references for at least the same reasons stated above in connection with Claims 44, 86 and 99 and are therefore believed to be in condition for immediate allowance. Furthermore, these claims are amended such that Applicants peptides are distinguishable from that of Barbas PCT in that they have agnostic properties, i.e. bind to a target while exhibiting the biological activity of the biologically active peptide, and not merely binding to and blocking a binding site.

In view of the foregoing amendments and remarks, this case is believed to be in condition for allowance. Such early and favorable action is earnestly solicited.

Respectfully submitted,



Peter DeLuca
Reg. No. 32,978
Attorney for Applicants

Carter, DeLuca, Farrell & Schmidt, LLP
445 Broad Hollow Road - Suite 225
Melville, New York 11747
(631) 501-5700
(631) 501-3526 (fax)